original reports

Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non–Small-Cell Lung Cancer

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abstract

PURPOSE RTOG 0617 compared standard-dose (SD; 60 Gy) versus high-dose (HD; 74 Gy) radiation with concurrent chemotherapy and determined the efficacy of cetuximab for stage III non–small-cell lung cancer (NSCLC).

METHODS The study used a 2 × 2 factorial design with radiation dose as 1 factor and cetuximab as the other, with a primary end point of overall survival (OS).

RESULTS Median follow-up was 5.1 years. There were 3 grade 5 adverse events (AEs) in the SD arm and 9 in the HD arm. Treatment-related grade ≥3 dysphagia and esophagitis occurred in 3.2% and 5.0% of patients in the SD arm *v* 12.1% and 17.4% in the HD arm, respectively ($P = .0005$ and $< .0001$). There was no difference in pulmonary toxicity, with grade ≥3 AEs in 20.6% and 19.3%. Median OS was 28.7 *v* 20.3 months ($P = .0072$) in the SD and HD arms, respectively, 5-year OS and progression-free survival (PFS) rates were 32.1% and 23% and 18.3% and 13% ($P = .055$), respectively. Factors associated with improved OS on multivariable analysis were standard radiation dose, tumor location, institution accrual volume, esophagitis/dysphagia, planning target volume and heart V5. The use of cetuximab conferred no survival benefit at the expense of increased toxicity. The prior signal of benefit in patients with higher H scores was no longer apparent. The progression rate within 1 month of treatment completion in the SD arm was 4.6%. For comparison purposes, the resultant 2-year OS and PFS rates allowing for that dropout rate were 59.6% and 30.7%, respectively, in the SD arms.

CONCLUSION A 60-Gy radiation dose with concurrent chemotherapy should remain the standard of care, with the OS rate being among the highest reported in the literature for stage III NSCLC. Cetuximab had no effect on OS. The 2-year OS rates in the control arm are similar to the PACIFIC trial.

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INTRODUCTION

The initial report of RTOG 0617 was previously published.[1] The purpose of this article is to report long-term follow-up, complete with a 5-year survival analysis. Some important parameters that predict overall survival (OS) reported in the previous multivariable analysis were heart dose, tumor volume, institution accrual volume, and esophagitis/dysphagia score. For heart dose, we used both V5 and V30 metrics, which represent the heart volume that received 5 or 30 Gy of radiation, respectively. Both were significant for OS on the prior multivariable analysis and have triggered subsequent queries into RTOG 0617 and other data sets. An update of the multivariable analysis for OS is included, which verifies the importance of these parameters. Since this trial was first reported, the standard of care for patients with inoperable stage III non–small-cell lung cancer (NSCLC) has changed. The PACIFIC trial demonstrated an OS advantage for all patients, regardless of PD-L1 status, with the addition of durvalumab.[2] We include a perspective on comparisons between RTOG 0617 and PACIFIC, as have invariably occurred, because both trials now represent standards in radiation therapy (RT) and immunotherapy, respectively, for this patient population.

METHODS

Outcomes

The specified coprimary objectives of this trial were to compare the OS of patients treated with 74-Gy (high dose [HD]) *v* 60-Gy (standard dose [SD]) conformal RT (CRT) with concurrent chemotherapy and to compare

ASSOCIATED CONTENT

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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the OS of patients treated with cetuximab versus without cetuximab. A number of secondary objectives included a comparison of progression-free survival (PFS) and locoregional tumor control, a comparison of toxicity between SD and HD and between cetuximab and no cetuximab, and an assessment of patient-reported quality of life in each arm.

Eligibility criteria have been previously reported. Patients were randomly assigned to 1 of 4 treatment arms: HD versus SD with concurrent and consolidation chemotherapy with or without cetuximab. Of note, specific mutational analyses were not collected. All patients were required to read and sign an institution review board–approved informed consent document.

RT was delivered 5 days/week in 2-Gy fractions. The radiation dose, fractionation, treatment planning, and treatment techniques have been previously described. Institutional credentialing was performed because this was the first National Cooperative Trial Network study to use intensity-modulated RT (IMRT) for lung cancer. RT plan review and compliance were described previously. Chemotherapy consisted of weekly paclitaxel (45 mg/m^2/week) and carboplatin (area under the curve [AUC], 2/week) during RT. Two weeks after chemoradiation, 2 cycles of consolidation chemotherapy separated by a 3-week interval were administered that consisted of paclitaxel (200 mg/m^2) and carboplatin (AUC, 6). Patients in the cetuximab groups received the agent during both concurrent and consolidative phases. Cetuximab was given at 400 mg/m^2 intravenously on day 1, with concurrent chemoradiation starting on day 8. Weekly cetuximab dosing was 250 mg/m^2 given before chemotherapy and RT that day. Consolidation cetuximab (250 mg/m^2/week) was given weekly during consolidation.

Follow-up evaluations were to be performed every 3 months for year 1, every 4 months for year 2, every 6 months for years 3-5, and then annually. Computed tomography (CT) scans were to be done every 6 months for the first 2 years and then annually. All data were collected by the enrolling site and then reported to RTOG through standard case report forms.

The trial was a 2 $\times$ 2 factorial design, with RT dose as 1 treatment factor and cetuximab as the other. A log-rank test for each factor at 1-sided α = .0125 (α = .0250 for both factors to account for multiple comparisons) would provide a statistical power of 80% to detect an improvement in median OS from 17.1 to 24 months after 339 deaths were reported from a total sample of 500 patients. Three interim analyses with early stopping criteria using Haybittle-Peto boundaries[3,4] for efficacy and Freidlin and Korn[5] methods for futility were planned after 85, 170, and 225 events and overseen by the independent RTOG data monitoring committee. All adverse events (AEs) were graded using the Common Terminology Criteria for Adverse Events (version 3.0); response was evaluated per RECIST.[6,7] Results are reported on a modified intention-to-treat basis, with all patients included in the assigned arm irrespective of treatment received but excluding those patients found not to have met the predefined eligibility criteria. End points of OS, PFS, local failure, and distant metastasis were measured from the date of random assignment. OS and PFS were estimated by the Kaplan-Meier method,[8] compared using the log-rank test,[9,10] and modeled using the Cox proportional hazards method.[10] The cumulative incidence method[11] was used to estimate local failure and distant metastasis rates, which were compared using Gray's test[12] and modeled using the Fine and Gray[13] method. Categorical data were compared using χ^2 test; continuous data were compared using *t* tests or Wilcoxon rank sum tests, as appropriate. Two-sided *P* values are reported throughout. All analyses were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC) except for the Fine and Gray modeling, which was performed using R (R Project for Statistical Computing, Vienna, Austria). At the first interim analysis in June 2011, the monitoring committee determined that the trial had crossed the futility boundary with respect to HD radiation. The HD radiation arms were then closed, and the trial continued to accrue patients to the 60-Gy with or without cetuximab arms. At the third interim analysis in June 2013, it was likewise determined that a futility boundary with respect to cetuximab had been crossed.

Random Assignment and Masking

Treatment arms were assigned using the permuted block randomization scheme described by Zelen[14] and stratified by RT technique (3-dimensional [3D] CRT *v* IMRT), Zubrod performance status at the time of enrollment (0 *v* 1), use of positron emission tomography (PET) during tumor staging (no *v* yes), and histology (squamous *v* nonsquamous). The trial design, data collection, analysis, interpretation of data, and writing of the report were the responsibility of the authors. The National Cancer Institute approved the trial design, monitored trial progress, and received the 2 interim futility analyses of both the RT and the cetuximab end points. Bristol-Myers Squibb agreed to the initial trial design and received the data reports for both the RT and the cetuximab end points. An NRG Oncology statistician had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

Of the 544 patients accrued, 496 were eligible for analysis. Figure 1 shows the CONSORT diagram. The median follow-up for all evaluable patients was 2.7 years and for surviving patients, 5.3 years (interquartile range, 4.7-6.1 years). Patient, tumor, and treatment characteristics were described in the primary article.[1] With respect to random assignment by radiation dose, there were 3 grade 5 AEs in

the SD arm and 9 in the HD arm that were attributed to treatment. One additional patient died since the initial publication secondary to an upper GI hemorrhage. All grade 5 toxicity events are listed in Table 1. Grade ≥ 3 treatment-related AEs are listed in Table 2. In the SD arm, 76.6% of patients *v* 79.7% in the HD arm experienced grade ≥ 3 treatment-related AEs ($P = .44$). In the SD arm, 7 patients (3.2%) experienced grade ≥ 3 dysphagia *v* 25 (12.1%) in the HD arm. Eleven patients (5.0%) in the SD arm and 36 (17.4%) in the HD arm experienced grade ≥ 3 esophagitis, including 1 grade 5 AE. After combining esophagitis and dysphagia, 16 patients (7.3%) in the SD arm and 43 (20.8%) in the HD arm experienced 1 or both toxicities ($P < .0001$). No statistical difference was found in overall pulmonary toxicity, with grade ≥ 3 AEs occurring in 20.6% and 19.3%, respectively. Since the primary publication, 1 additional patient in the SD arm experienced grade ≥ 3 pneumonitis. With respect to cetuximab random assignment, 71.2% of the patients in the no cetuximab arm and 87.3% of patients in the cetuximab arm experienced grade ≥ 3 treatment-related AEs ($P < .0001$).

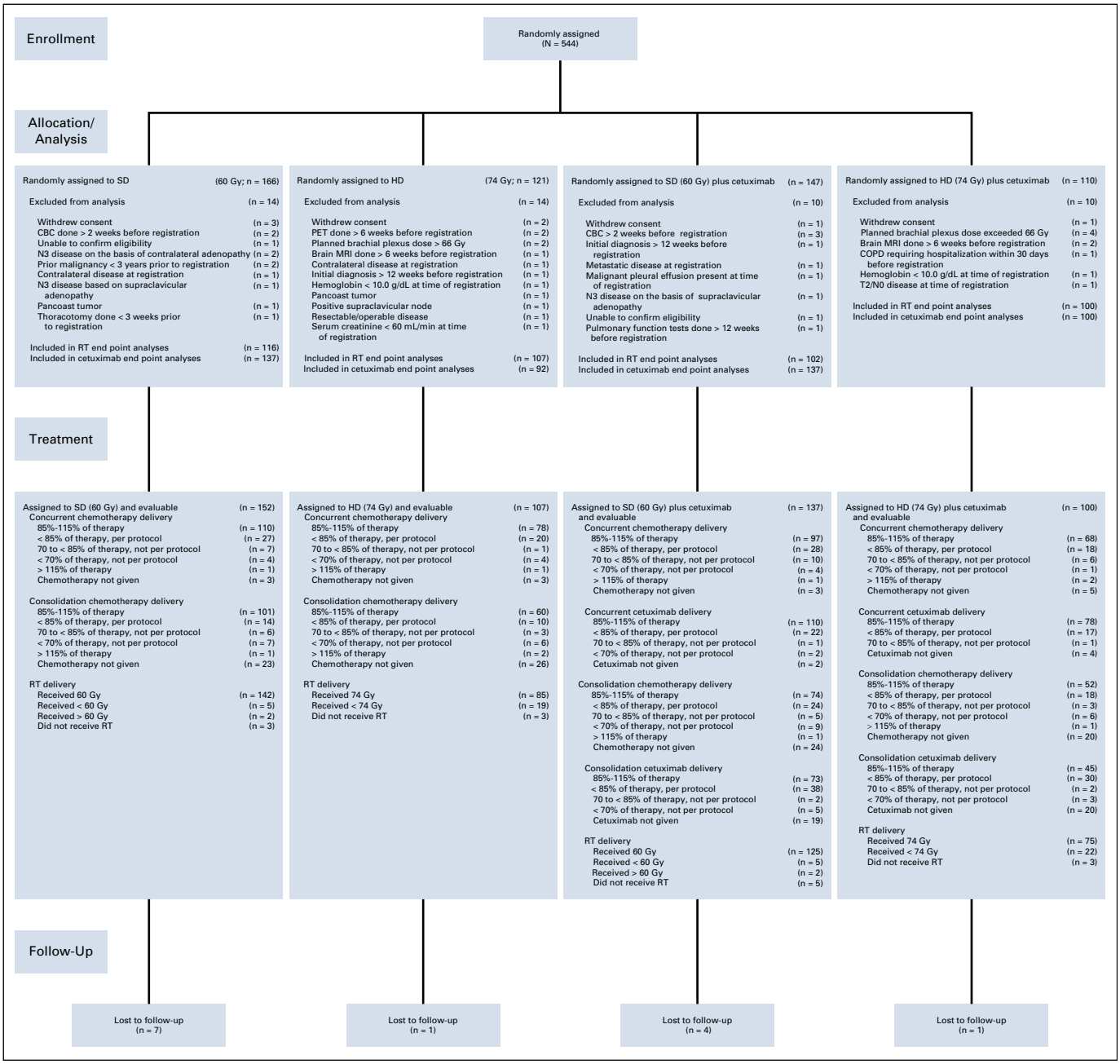

FIG 1. RTOG 0617 CONSORT diagram. COPD, chronic obstructive pulmonary disease; HD, high dose; MRI, magnetic resonance imaging; PET, positron emission tomography; RT, radiation therapy; SD, standard dose.

TABLE 1. Grade 5 Adverse Events

Assigned Treatment	Category	Term	Related to Treatment?	Days Since Start of Treatment	Days Since End of Treatment
Arm A: 60 Gy	Pulmonary/upper respiratory	Dyspnea	Unlikely	130	46
	Death	Death	Unlikely	172	89
	Pulmonary/upper respiratory	Pneumonitis	Possibly	176	91
	Hemorrhage/bleeding	Pulmonary hemorrhage	Unrelated	114	28
Arm B: 74 Gy	Vascular	Thrombosis	Unlikely	103	33
	Infection	Pneumonia (with unknown ANC)	Unrelated	627	508
	Pulmonary/upper respiratory	Respiratory disorder	Probably	775	677
	Death	Disease progression	Unlikely	62	7
	Vascular	Thrombosis	Unrelated	88	33
	GI	Acquired tracheo-esophageal fistula	Definitely	710	612
	Infection	Pneumonia (with normal or grade 1-2 ANC)	Unlikely	83	40
	GI	Acquired tracheo-esophageal fistula	Unrelated	1,236	1,145
	Death	Sudden death	Unlikely	105	7
	Pulmonary/upper respiratory	Respiratory disorder	Possibly	115	10
	Death	Disease progression	Possibly	216	158
Arm C: 60 Gy plus cetuximab	Death	Sudden death	Possibly	109	11
	Hemorrhage/bleeding	Pulmonary hemorrhage	Unlikely	30	1
	Pulmonary/upper respiratory	Pneumonitis	Probably	159	54
	Vascular	Thrombosis	Unlikely	120	15
	Cardiac general	Myocardial ischemia	Unlikely	98	0
	Hemorrhage/bleeding	Upper GI hemorrhage	Definitely	1,061	955
	Death	Sudden death	Unrelated	54	4
	Death	Death	Unrelated	65	12
	Hemorrhage/bleeding	Respiratory tract hemorrhage	Probably	67	4
	Death	Death	Unlikely	798	742
	Pulmonary/upper respiratory	Pneumonitis	Probably	68	22
	Infection	Febrile neutropenia	Definitely	85	7
	Pulmonary/upper respiratory	Respiratory disorder	Probably	65	15
Arm D: 74 Gy plus cetuximab	Hemorrhage/bleeding	Upper GI hemorrhage	Possibly	215	88
	Vascular	Thrombosis	Probably	95	43
	Cardiac arrhythmia	Supraventricular tachycardia	Unlikely	204	85
	Hemorrhage/bleeding	Esophageal hemorrhage	Unrelated	680	568
	Infection	Sepsis (with normal or grade 1-2 ANC)	Unlikely	438	326
	Infection	Pneumonia (with unknown ANC)	Probably	131	19
	Cardiac general	Cardiac disorder	Unrelated	415	303

(continued on following page)

TABLE 1. Grade 5 Adverse Events (continued)

Assigned Treatment	Category	Term	Related to Treatment?	Days Since Start of Treatment	Days Since End of Treatment
	Vascular	Thrombosis	Unlikely	14	1
	Hemorrhage/bleeding	Pulmonary hemorrhage	Possibly	56	1
	GI	Esophagitis	Probably	193	116
	Death	Death	Unrelated		

NOTE. Adverse events were graded with Common Terminology Criteria for Adverse Events (version 3.0).
Abbreviation: ANC, absolute neutrophil count.

Compliance with RT protocol was reported previously and remained unchanged. The SD arms were more protocol compliant than the HD arms (83% *v* 74%, respectively; $P = .0235$). However, as also previously published, an analysis of the SD and HD arms restricted to plans that were per protocol showed nearly identical results to the overall analysis. The percent planning target volume (PTV) covered by 95% of the prescription dose as well as 100% of the prescription dose was significantly better in the SD arms ($P < .0001$). The minimum margin between PTV and clinical target volume was smaller in the HD arm ($P = .005$). For the HD arm, the median minimum margin was 3.9 mm (range, 0-9.8 mm), whereas the SD arm had a median minimum margin of 4.5 mm (range, 0.0-9.8 mm). There was no difference in OS with IMRT, which was previously reported.[15]

With respect to radiation dose, the median OS was 28.7 *v* 20.3 months (2-sided $P = .0072$) for the SD versus HD arms, respectively. The 5-year OS rates were 32.1% *v* 23.0% (2-sided $P = .007$), which favored the SD arm (Fig 2). The hazard ratio (HR) for OS was 1.35 (95% CI, 1.08 to 1.69). The 5-year PFS rates were 18.3% *v* 13.0% (2-sided $P = .055$), which favored the SD arm (Fig 3). The median PFS was 1.0 year (95% CI, 0.8 to 1.2 years) in the SD arm and 0.8 years (95% CI, 0.7 to 1.0) in the HD arm (2-sided $P = .055$). The corresponding HR was 1.22 (95% CI, 1.00 to 1.51). The primary cause of death, reported by the treating institution, was primary lung cancer (SD arm, 71.3%; HD arm, 71.8%). The 5-year pattern-of-failure rates are listed in Table 3. No statistical differences were found in failure patterns by radiation dose arm. Secondary cancers occurred in 26 patients (6.1%) overall (7.3% *v* 4.8% in the SD and HD arms, respectively). Salvage therapies were reported for 281 randomly assigned patients with either recurrent lung cancer or secondary other cancers (56.7%). Salvage therapy could consist of any combination of surgery, chemotherapy, and/or RT because immunotherapy was not scored. Salvage surgery was performed in 49 patients (13%), chemotherapy in 187 (50%), and additional RT in 138 (37%).

The multivariable analysis findings for OS are listed in Table 4. Factors that affected OS were radiation dose, tumor location, institution accrual volume, esophagitis/dysphagia, PTV, and heart V5. Heart V5 was chosen for this analysis because nearly all patients had heart V5 values. Substitution of heart V30 for heart V5 provided similar multivariable analysis results. A separate analysis with regard to the impact of radiation dose to the heart and heart substructures from this trial is forthcoming. The use of cetuximab conferred no survival benefit. Median OS with or without cetuximab was 2 years for each (2-sided $P = .977$). Significantly more patients in the cetuximab arm experienced grade ≥ 3 treatment-related AEs (87.3% *v* 71.2%). Likewise, cetuximab conferred no PFS benefit or any difference in failure patterns. The prior signal of cetuximab benefit in patients with H scores ≥ 200 was no longer apparent, with a median OS of 2.9 years with cetuximab and 1.8 years without (2-sided $P = .14$).

Patients included in the SD arm analyses of RTOG 0617 were examined for comparison with the outcomes of the PACIFIC trial, which added a maintenance anti-PD-L1 agent, durvalumab. Those patients whose cancer had progressed within the first follow-up imaging time point were excluded. Only 2.2% of patients had progressed and were excluded from this subset analysis. An

TABLE 2. Maximum Treatment-Related Adverse Events by Arm

	Arm, No. (%)			
Adverse Event	A: 60 Gy (n = 152)	B: 74 Gy (n = 107)	C: 60 Gy + Cetuximab (n = 137)	D: 74 Gy + Cetuximab (n = 100)
No grade ≥ 3 toxicity	42 (27.6)	32 (29.9)	20 (14.6)	10 (10.0)
Grade ≥ 3 toxicity	110 (72.4)	75 (70.1)	117 (85.4)	90 (90.0)
*P**	.0002			

*χ^2 test, 2-sided.

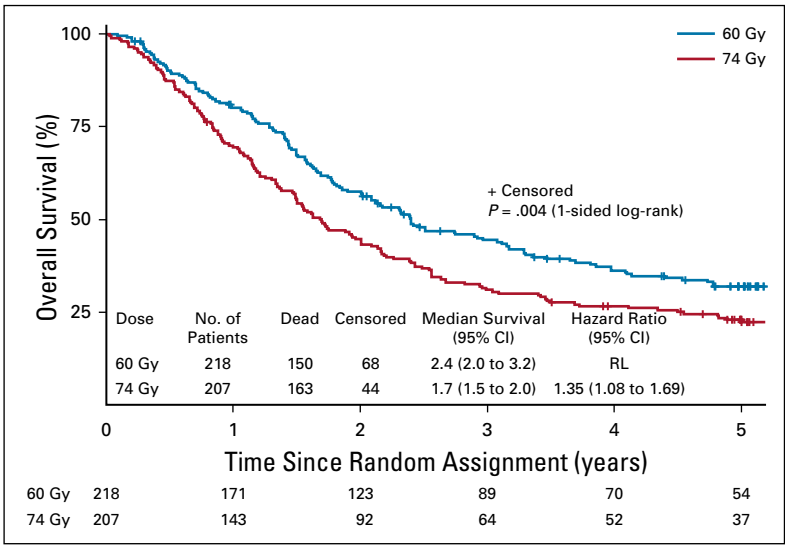

FIG 2. Overall survival by radiation therapy dose. RL, reference level.

additional 2.4% of patients died without progression within the initial chemoradiation time point. Thus, to parallel the PACIFIC randomization strategy, 4.6% of patients in the SD arm of RTOG 0617 would not have been included in the survival results reported in the PACIFIC trial. The 2-year landmark OS and PFS rates for this subset of RTOG 0617 were 59.6% (95% CI, 52.6% to 66.0%) and 30.7% (95% CI, 24.6% to 37.1%), respectively. This compares to 66.3% (95% CI, 61.7% to 70.4%) and 49.5% (95% CI, 44.6% to 54.2%), respectively, in the maintenance immunotherapy arm of PACIFIC.[16] Thus, the 2-year OS rates seem to be similar between trials, but the PFS rates in PACIFIC appear to be better. A comparison of the chemoradiation-only (control) arms of both studies indicates that OS for the RTOG 0617 SD arm may be superior (59.6% *v* 49.5%) and suggests that there may be issues with RT quality in the PACIFIC trial, which did not collect RT data for quality assurance purposes.

DISCUSSION

The 5-year OS estimate for the SD radiation arm of RTOG 0617, regardless of cetuximab delivery, was 32.1%. This is among the highest OS results of any phase III trial for patients with stage III NSCLC. These results argue strongly that the current standard-of-care radiation dose should be 60 Gy given in 2-Gy daily fractions to a target volume directed at tumor plus margin on the basis of CT and PET/CT, excluding elective nodal irradiation.

After the release of the initial results of this trial, many have surmised that RT noncompliance may have contributed to the poorer outcome on the HD arms, yet there was no difference in outcomes when analyzing the protocol-compliant population versus the overall population. From our initial publication, trial RT compliance was 90%. We used rigorous RT quality assurance for this trial, which required that each participating center have credentials for either 3D-CRT or IMRT, whichever they

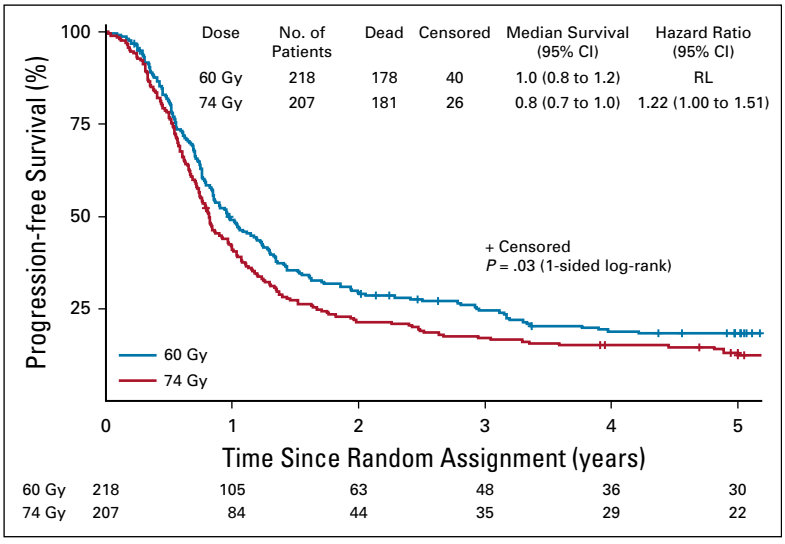

FIG 3. Progression-free survival by radiation therapy dose. RL, reference level.

TABLE 3. Patterns of Failure at 5 Years

	Standard Dose (60 Gy)		High Dose (74 Gy)		
Failure Pattern	**Failed, % (95% CI)**	**No. at Risk**	**Failed, % (95% CI)**	**No. at Risk**	***P***
Local	38.2 (31.7 to 44.8)	40	45.7 (38.7 to 52.4)	27	.07
Regional	35.7 (29.3 to 42.2)	37	38.4 (31.7 to 45.0)	27	.54
Locoregional	49.7 (42.8 to 56.3)	34	55.4 (48.3 to 61.9)	25	.17
Distant	52.3 (45.3 to 58.8)	36	57.6 (50.4 to 64.1)	24	.32

chose to use, and each patient's dosimetry was reviewed centrally. This provides confidence that the results are not due to poor RT compliance. NRG Oncology continues to value central RT quality assurance review within its RT trial portfolio.

Local control is important toward improving cure rates. Thus, radiation dose intensification continues to be a focus of clinical trials. From this RTOG experience, where a higher radiation dose delivered with concurrent chemotherapy was detrimental, factors predictive of better OS on multivariable analysis include tumor locations away from the heart,[17] treatment at centers with higher enrollment volumes,[18] smaller PTVs (or gross tumor volumes), and reduction of the heart dose as much as possible. We previously published a planned secondary analysis comparing 3D-CRT with IMRT that showed that the use of IMRT resulted in less toxicity, particularly pneumonitis.[15] However, no OS difference was detected between these 2 delivery techniques.

Other means to intensify radiation dose are being tested in ongoing early-phase clinical trials. Such efforts include the use particle therapy, adaptive therapy, isotoxicity dose prescriptions, and stereotactic body RT boosts. Phase I and II trials in proton therapy are attempting to hypofractionate radiation dose, with a focus on the ability of protons to limit normal tissue dose.[19] Another ongoing phase III trial that is comparing photons to protons (RTOG 1308) allows a higher dose of 70 Gy to be delivered on either arm when normal tissue dose constraints are met. RTOG 1106 has completed accrual, but results have not yet been reported. This study used a midtreatment PET/CT to allow a hypofractionated boost over the last 2 weeks to escalate radiation dose to residual cancer. Chinese investigators have reported results of a similar study, a phase II randomized trial that tested a PET-adapted shrinking field and simultaneous integrated boost technique against conventional RT. This randomized phase II trial suggested an OS and PFS benefit when using a PET-adapted simultaneous boost technique.[20] van Diessen et al[21] reported higher rates of acute and late toxicity in a randomized phase II dose escalation trial that used a PET boost. The base radiation scheme to the entire tumor volume was ≥ 72 Gy in 24 fractions (≥ 3 Gy/fraction). In addition, an isotoxicity boost was given concurrently to regions with a maximum standardized uptake value of > 50%. Nine of 107 randomly assigned patients in this trial experience fatal toxicity. A number of German institutions have completed accrual for a phase III trial on fluorodeoxyglucose-PET–guided target volume reduction for isotoxic dose escalation in locally advanced NSCLC. The researchers have enrolled patients with locally advanced lung cancer who are receiving chemoradiation and have randomly assigned them to conventional target volumes versus PET-only target volumes and are allowing doses up to 74 Gy if strict normal tissue doses are achieved. The primary end point is local progression, but the results have not been reported. As radiation dose intensification trials continue, perhaps total dose and fraction size should take tumor

TABLE 4. Multivariable Cox Model of Overall Survival

Covariate	**Comparison**	**Dead of Total RL**	**Dead of Total Group 2**	**HR (95% CI)**	***P****
Radiation level	Standard dose (RL) *v* high dose	132 of 196	147 of 188	1.300 (1.020 to 1.660)	.0315
Tumor location	LLL or central node (RL) *v* neither LLL nor central node	172 of 226	107 of 158	0.860 (0.607 to 1.110)	.2395
Institution accrual volume	1-3 patients (RL) *v* ≥ 4 patients	122 of 149	157 of 235	0.740 (0.580 to 0.950)	.0170
Maximum related esophagitis/dysphagia grade	Maximum grade < 3 (RL) *v* maximum grade ≥ 3	230 of 328	49 of 56	1.540 (1.120 to 2.120)	.0079
Volume of PTV (log-transformed)	Continuous	279 of 384		1.323 (1.041 to 1.680)	.0219
Heart V5	Continuous	279 of 384		1.008 (1.002 to 1.013)	.0051

NOTE. Heart V5 is based on heart contour performed centrally at NRG Oncology.[17]

Abbreviations: HR, hazard ratio; LLL, lower-left lobe; PTV, planning target volume; RL, reference level.

*Two-sided.

volume and location into account because large central tumors have been shown to be a higher risk than others. For example, techniques using proton beam may be more beneficial for patients with tumors adjacent to the heart.

The landscape for the management of locally advanced NSCLC is changing rapidly. The standard of care has changed to include the anti-PD-L1 agent durvalumab as consolidation therapy after completion of chemoradiation, regardless of the patient's PD-L1 biomarker status.[2] The OS results have been published.[16] For OS, the HR was 0.68 in favor of the experimental durvalumab arm. One-year, 2-year, and median OS results were 83.1%, 66.3%, and not reached, respectively (P = .003). For PFS, the HR was 0.51, with 1-year, 2-year, and median PFS results of 55.7%, 49.5%, and 17.2 months, respectively. Specific to this trial, patients were randomly assigned after completion of chemoradiation, which means that those who progressed or were not eligible for durvalumab because of poor health were not randomly assigned. Thus, PACIFIC patients were more selected by the randomization process that occurred after chemoradiation in those who presumably were able to tolerate anti-PD-L1 therapy. Using the RTOG 0617 SD arm data, the rate of being removed from therapy after CRT was 4.6%. The RTOG 0617 and PACIFIC data viewed in this manner indicate that the OS results are similar (59.6% *v* 66.3%), which anticipates an approximate 5% benefit with the use of consolidation immunotherapy. PACIFIC also seems to have a higher PFS rate (30.7% *v* 49.5%). The PACIFIC data will need to be monitored longer term to further estimate the statistical design impact of randomly assigning patients after completion of CRT. One concern about PACIFIC is that quality assurance data on RT were not collected, so one cannot estimate whether RT quality had an impact on outcomes. High-quality image-guided RT would be likely to improve outcomes further in the setting of future immunotherapy trials.

In conclusion, the 5-year OS rate for patients in the SD RT arm of RTOG 0617 was 32.1%, a new 5-year landmark in long-term OS of patients with unresectable stage III NSCLC. The use of cetuximab conferred no benefit or harm. Future studies will be focused on improving both RT and systemic therapy.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Long-Term Results of NRG Oncology RTOG 0617: Standard- Versus High-Dose Chemoradiotherapy With or Without Cetuximab for Unresectable Stage III Non–Small-Cell Lung Cancer

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